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Ginger G. Grammer 11/3/05
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No.:	10/047,578
Filing Date:	October 26, 2001
Applicants:	Jeffrey S. Kiel et al.
Title:	PHENYLEPHRINE TANNATE AND PYRILAMINE TANNATE SALTS IN PHARMACEUTICAL COMPOSITIONS
Art Unit:	1614
Examiner:	Brian Kwon
Confirmation No.:	1696
Attorney Docket:	PEDI-04 (formerly KIEL-02)

Cincinnati, Ohio November 3, 2005

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF H. GREG THOMAS UNDER 37 C.F.R. § 1.132

1) I am H. Greg Thomas, Ph.D. I reside at 700 Bethesda Church Road, Carrollton, Georgia 30117. I am listed as a coinventor of U.S. Patent Application Serial No. 10/047,578.

2) I received a B.A. degree in Chemistry from the State University of West Georgia in 1978 and a Ph.D. from the University of Georgia, College of Pharmacy, Department of Medicinal Chemistry in 1983. I was a Senior Manager, Analytical Development, and

Principal Scientist of Drug Disposition and Safety at Solvay Pharmaceuticals from 1989-1997. Prior to 1989, I was an Associate of Medicine/Principle Investigator at Emory University and the Veterans Administration Medical Center in Atlanta, Georgia. I joined Kiel Laboratories, Inc. in 1998 as Director of Laboratory Services. In 2000, I assumed the responsibility of Vice President of Research and Development, and currently oversee formulation projects, analytical method development and validation, clinical trials, and regulatory submissions. I have authored more than 25 publications and presentations, and served as Peer Reviewer for two journals.

3) I have carefully reviewed and considered U.S. Patent Application Serial No. 10/047,578 ("the '578 application"), the Office Action dated May 4, 2005, issued in the '578 application, and U.S. Patent Nos. 5,599,846 ("Chopdekar") and 6,287,597 ("Gordziel") cited by the Examiner in that Office Action to support the rejection of the claims presented in the '578 application.

4) This Declaration is provided in order to illustrate the unique and nonobvious nature of the tannate salt conversion process and compositions prepared thereby, which are the subjects of the '578 application. The information provided herein should not in any way be construed as limitations of the process or composition of the '578 application.

5) Both Chopdekar and Gordziel describe processes for the preparation of tannate forms of pyrilamine and/or phenylephrine, which then may be used to prepare compositions including those tannate forms of pyrilamine and/or phenylephrine. In my opinion, and as discussed in greater detail below, the use of those pyrilamine tannate and/or phenylephrine tannate forms to prepare compositions including same, results in compositions that exhibit greater variability of amounts of active ingredients in each batch or dosage unit of the final composition as compared to the presently claimed composition, which is prepared by the method recited in those claims.

6) The claimed composition of the '578 application includes liquid, solid, or semi-solid dosage forms containing a tannate salt complex of active pharmaceutical ingredients ("API"). The composition, as recited in the claims, is prepared by a conversion method which includes the steps of mixing a dispersing agent and tannic acid in a suitable solvent or diluent to generate a mixture in liquid or powder form. The API as a salt or in the free base form is combined with the dispersing agent/tannic acid mixture to generate the tannate salt complex. This complex is incorporated directly into a dosage form (such as a suspension or tablets). The presence of the dispersing agent prevents the clumping and aggregation of the tannate salt complex formed and aids in promoting uniformity of the API in the compositions formed.

7) Because the tannate molecule is a large molecule, the percentage of API, such as pyrilamine or phenylephrine, within the tannate salt is significantly lower than that in common salt forms such as the hydrochloride or maleate. Further, commercially available tannate salts vary widely in their purity. The presence of low percentages of API and the variable purity of the commercially available tannate salts leads to the stoichiometry of the API to tannic acid in the tannate salts to be different from batch to batch, and thus ultimately in dosage unit to dosage unit. This increases the likelihood that commercially available pharmaceutical products contain variable and in some instances sub-therapeutic levels of API, when compositions are prepared using the tannate salts, as in Chopdekar and Gordziel. Further, in my experience as a medicinal chemist, an increase in the uniformity of the amounts of API in the tannate salts, such as would be used in Chopdekar and Gordziel, would require further processing of the tannate salts.

8) The claimed compositions of the '578 application, however, contain tannate salts of active ingredients that are prepared with reduced variability in API and increased certainty that the API are delivered within a therapeutic range. This is accomplished by starting with a known amount of commonly available salt or the free base form of the API, which is subsequently converted and incorporated in situ as a tannate salt. Since the tannate salt of the API is generated and incorporated in situ into the dosage form during the manufacturing process, the purification and drying steps required for the

isolation of the tannate salt are eliminated and the stoichiometry of the tannate salt is generally uniform from batch to batch. Thus, the invention provides a composition by an efficient and reproducible method to manufacture products containing tannate salts as active ingredients.

9) To demonstrate this further, attached as Exhibit A hereto are commercial specifications for pyrilamine tannate and phenylephrine tannate. Attached as Exhibit B hereto are USP specifications for salt forms of pyrilamine and phenylephrine. A comparison of the specifications provided in Exhibits A and B provides a content variation comparison between active ingredient raw materials used during the manufacture of tannate pharmaceutical compositions, such as those described in Chopdekar and Gordziel, versus that of the presently claimed composition, which uses the method recited in the composition claims of the '578 application. The information concerning content variability in pyrilamine tannate and phenylephrine tannate was obtained from Cadila Pharmaceuticals, Ltd.'s published specifications and is typical of that in the art. The information concerning content variability in common salt raw materials, (pyrilamine maleate and phenylephrine hydrochloride), which is typical of that in the art, was obtained from the USP, which is the source of industry-accepted specifications.

10) The content variation for the common salt of pyrilamine (pyrilamine maleate) is 2.50% (98%-100.5%), whereas the content variation range for the tannate salt of pyrilamine is 6% (41%-47%). The content variation range for the common salt of phenylephrine (phenylephrine hydrochloride) is 5% (97.5%-102.5%). The content variation range for the tannate salt of phenylephrine is 9% (26%-37%). In each case, there is more variation in the active ingredient added to the formulation as tannate salt and processed into finished pharmaceutical compositions, such as those set forth in Chopdekar and Gordziel. The decrease in active ingredient variability inherent in the claimed compositions due to the use of the method recited in the claims would be 3.50% for pyrilamine and 4% for phenylephrine. In the manufacture of pharmaceutical products, these are very significant reductions in content variability.

11) Chopdekar and Gordziel, however, do not use the method recited in the composition claims of the '578 application. Rather, they isolate a tannate salt, such as by converting the free-base form to the tannate salt, and thereafter process those tannate salts into a composition. Thus, in order for Chopdekar and Gordziel to achieve the same level of API uniformity as would be exhibited by the composition of the '578 application, a correction in the amount added to the formulation must be made each time a batch is prepared using a different lot of tannate salt raw material. In fact, such a correction must be performed if the finished composition is to meet current international pharmaceutical product standards of 95%-105% of the target active ingredient amount.

Failure to do so may result in a subpotent and unmarketable product. The necessity of performing such a calculation decreases the efficiency of the manufacturing process and introduces another possible source of error, which could still result in content variability greater than the claimed composition of the '578 patent.

12) The general cause of increased content variability that is inherently produced in Chopdekar and Gordziel is not difficult to explain. Each step or operation performed in a manufacturing environment introduces some level of variability into the finished product. When the operation in question, such as a method of Chopdekar and Gordziel, involves isolating a tannate salt, such as by beginning with the free-base form and then converting to the tannate salt, and thereafter processing those tannate salts into a composition, the variability is focused on the amount of active ingredient contained in the finished pharmaceutical product. By eliminating the additional isolation step required by the prior art that is a potential source of increased content variability. the compositions as presently claimed are able to provide a consistently better finished product. Thus, by starting with a commonly available salt or free base of the active pharmaceutical ingredient, which is subsequently converted and incorporated in situ as a tannate salt complex, the invention provides an efficient and reproducible method to manufacture liquid or semi-solid products containing tannate salt complexes as active ingredients.

13) The decreased content variability that results in the claimed compositions due to the recited method has many real world advantages. A better-finished product in the pharmaceutical industry means a safer drug. The principal properties affected by converting a drug to the tannate salt form is solubility, which normally decreases after conversion to a tannate from a hydrochloride salt or bromide salt. The decreased solubility attained in this matter gives the drug prolonged action characteristics. Changes in the content of the tannate salt in a final drug product can potentially alter the overall amount of drug taken, as well as the rate at which the drug enters the body. Understandably, then, increased variability in drug content leads to increased risk to the patient taking the drug product. The need for increased safety and content uniformity is multiplied by the fact that many of the tannate drug products are designed for use by children.

14) I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Application Serial No. 10/047,578
Declaration under 37 CFR § 1.1.32
Reply to Office Action dated May 4, 2005

Further Declarant sayeth naught.

11/24/05
Date

H. Greg Thomas